

Aim of the study: To find differences between a group of patients with intraocular melanoma and another primary cancer and a group of patients with no identifiable second primary cancer.

Material and methods: The analysis involved 240 participants, selected from patients who were treated for uveal melanoma at the Department of Ophthalmology and Ocular Oncology of the Jagiellonian University Medical College between the year 1998 and 2007. Among those patients 97 were diagnosed with one or more independent primary cancers. Those patients were subject to a comparative analysis with a second group of 143 patients who had uveal melanoma with no identifiable second primary cancer.

Results: Statistically significant differences between the group of patients with intraocular melanoma and another primary cancer, and the group of patients with uveal melanoma (but without another diagnosed primary neoplasm) were as follows: more common family history of cancer, better education, living in cities (especially with a population over 500 thousand), previous surgery except for uveal melanoma, and two or less than two pregnancies in the case of women.

Conclusions: This analysis revealed that more common family history of cancer, better education, living in cities (especially with a population over 500 thousand), previous surgery, except for uveal melanoma, and two or less than two pregnancies in the case of women, were associated with a higher rate of detection of multiple primary cancers.

Key words: uveal melanoma, multiple primary cancers.

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The impact of selected factors on early diagnosis of multiple primary cancers in patients with uveal melanoma

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Introduction

Uveal melanoma is the most common primary intraocular cancer in adults [1]. The tumor occurs in approximately 4.3–7 cases per million per year [2–5] and comprises 2.9% of all melanomas [4].

Anomalies in chromosomes 1, 3, 6, 8, 13, 16, 18 in uveal melanoma have been described [6, 7]. The most common prognosis-affecting chromosomal disorders associated with the tumor include: loss of chromosome 1p, 3, 6q and 8p and an extra copy of chromosome 6p and 8q [6–9]. According to many authors monosomy 3 is associated with highly aggressive, rapidly progressive disease [7, 10–14].

There are some other reported cases of primary cancers in patients with uveal melanoma, but limited data exist regarding factors causing development of another primary cancers among the affected patients.

There are reports on development of other primary cancers of other organs available in the literature [15–17].

The problem of multiple primary cancers emerged as a medical issue already in the nineteenth century. Renaud in 1847 and Rokitansky in 1855 reported cases of two independent cancers [15].

The aim of the current analysis was to find differences between the group of patients with intraocular melanoma and another malignant neoplasm of different origin, and another group of patients with uveal melanoma but no other diagnosed primary cancer. Primary malignancies included skin cancers, colon cancer, skin melanoma, cancers involving the breast and genital tract in females and other less common cancers in our analysis.

Material and methods

Two hundred forty patients diagnosed and treated with uveal melanoma at the Clinic of Ophthalmology and Ocular Oncology of the Jagiellonian University Medical College in Kraków, Poland, from January 1998 to December 2007 were included in the analysis. The study group involved 97 patients with other primary malignancies; 57 (58.8%) patients were females and 40 (41.2%) were males. The patients' age ranged between 35 and 83, with a mean age of 63.2 ± 9.9 (Table 1).

Information about patients' current health condition and answers to questionnaires were obtained from 87 patients (51 women and 36 men) or their relatives. In other cases, data were analyzed on the basis of the medical history. The above-mentioned group was compared with another group of patients with uveal melanoma but without the diagnosis of another primary cancer. The control group consisted of 143 patients, 83 (58%) females and 60 (42%) males, aged 36–87 years, with a mean age of 59.6 ± 12.1 (Table 2).

The analysis was based on the clinical examination and data were obtained from patients (or their relatives) during a follow-up.

An analysis of the influence of factors including marital status, education, occupation, place and region of residence, smoking, alcohol consumption, exposure to sunlight, exposure to harmful chemicals, hormonal factors and a history of pregnancy, a history of surgery for treatment of unbound uveal melanoma and the presence of cancer in the family (on the occurrence of multiple primary cancers in patients with uveal melanoma) was performed.

Statistical analysis was performed using the χ^2 test, logistic regression and Kaplan-Meier survival curves. Statistical significance was accepted as $p < 0.05$.

Results

Patients with multiple primary cancers, compared to patients without the diagnosis of other primary malignancies, reported more commonly a family history of cancer in 1st degree relatives ($p = 0.0073$) and in 1st and/or 2nd degree relatives ($p = 0.0001$) (Figs. 1, 2).

Patients with multiple primary malignancies more often had secondary and higher education ($p = 0.0001$), more often worked [according to the ISCO-88 (COM) classification] as "professionals" ($p = 0.0001$) [18], were primarily city dwellers [as opposed to living in rural areas ($p = 0.0060$)], especially cities with a population over 500 thousand ($p = 0.0001$) [19], more frequently had a history of surgery unrelated to uveal melanoma ($p = 0.0000$), and – in the case of women – had fewer (≤ 2) pregnancies on average ($p = 0.0008$) (Figs. 3 [18], 4, 5 [19], 6, 7).

Logistic regression analysis revealed that the prevalence of multiple primary cancers in patients with uveal melanoma depended on a few above-mentioned factors: secondary and higher education, living in a city with a population of over 500 thousand, undergoing surgery, and a family history of cancer (in 1st and 1st and/or 2nd degree relatives). Patients' profession was not taken into consideration in logistic regression analysis, because this variable was dependent on the education. The number of pregnancies was not taken into consideration as well, because of its limitation to women (Table 3, 4).

The occurrence of other primary cancers among patients with uveal melanoma was not statistically significant

Table 1. Characteristics of the study group

| Gender | Number of patients | Mean age | Standard deviation |
|--------|--------------------|----------|--------------------|
| women | 57 (58.8%) | 61.6 | 9.8 |
| men | 40 (41.2%) | 65.0 | 9.9 |
| Total | 97 | 63.2 | 9.9 |

Table 2. Characteristics of the control group

| Gender | Number of patients | Mean age | Standard deviation |
|--------|--------------------|----------|--------------------|
| women | 83 (58.0%) | 59.3 | 11.8 |
| men | 60 (42.0%) | 60.0 | 12.6 |
| Total | 143 | 59.6 | 12.1 |

cantly associated with other individually analyzed factors listed above.

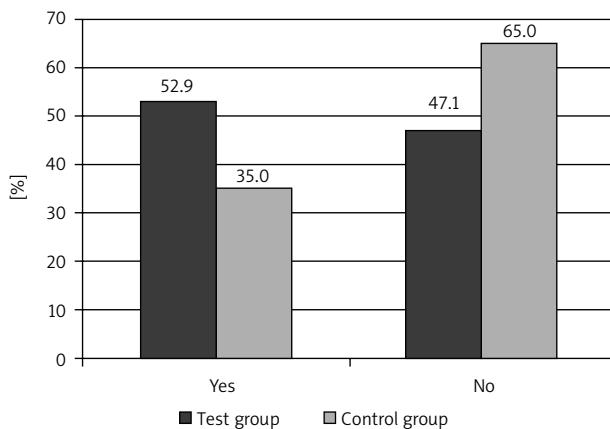
Discussion

Patients with multiple primary cancers, compared to patients without the diagnosis of other primary malignancies, reported more common family history of cancers among their relatives.

Abdel-Rahman *et al.* [20] observed that uveal melanoma patients with a family history suggesting a high risk of predisposition to a known cancer syndrome were at significantly higher risk for having a second cancer, compared to the remaining uveal melanoma patients.

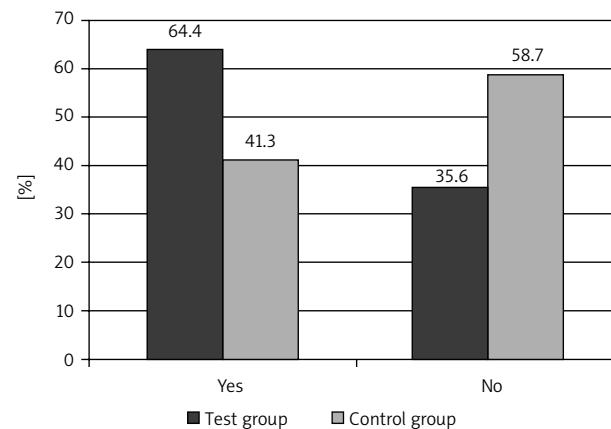
Bergman *et al.* [21] observed an increased risk of second primary cancers among Swedish patients with uveal melanoma but Callejo *et al.* [22] reported that in their Canadian cohort the statistical analysis showed no increased risk of a second cancer in patients with uveal melanoma.

That analysis showed that those patients' educational level had a significant effect on the diagnosis and the presence of multiple primary cancers. Those who had



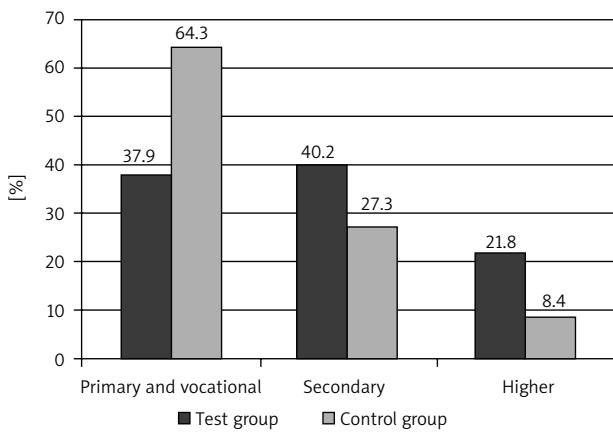
$p = 0.0073$

Fig. 1. Appearance of multiple primary cancers, depending on the occurrence of cancer among first degree relatives of patients



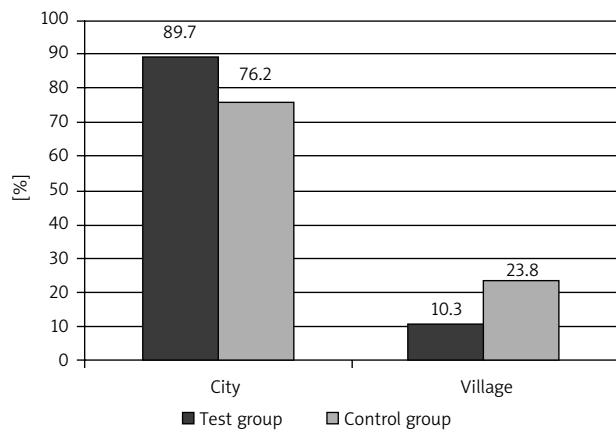
$p = 0.0001$

Fig. 2. Appearance of multiple primary cancers, depending on the occurrence of cancer among those patients' first and/or second degree relatives



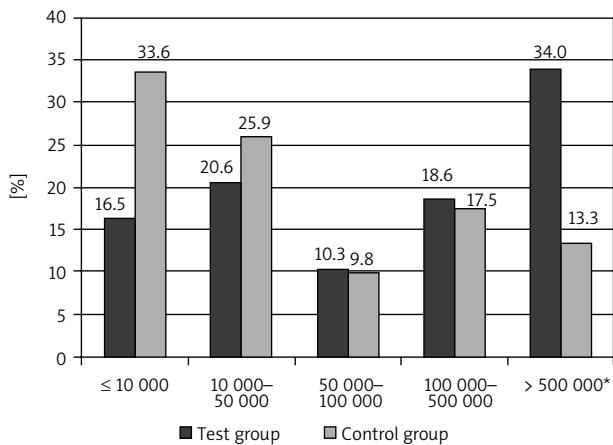
p = 0.0001 [18]

Fig. 3. Appearance of multiple primary cancers, depending on the level of education of patients



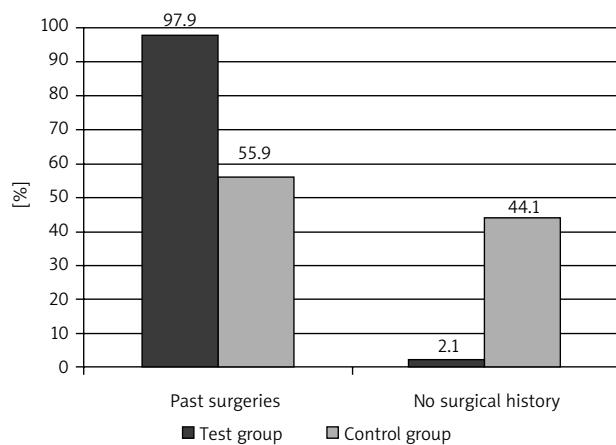
p = 0.0060 [19]

Fig. 4. Appearance of multiple primary cancers, depending on patients' place of living



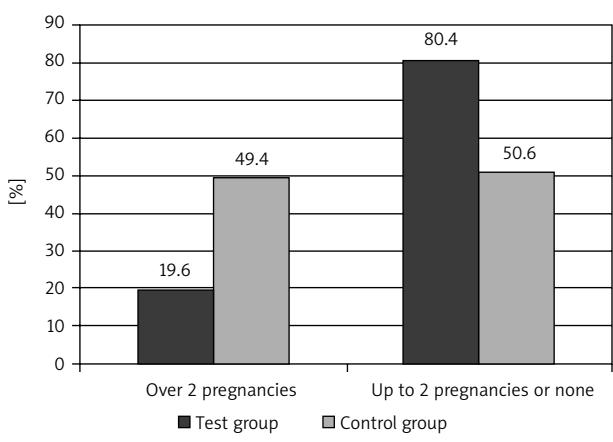
**p* = 0.0001 [19]

Fig. 5. Appearance of multiple primary cancers, depending on the place of residence, considering the population volume



p = 0.0000

Fig. 6. Appearance of multiple primary cancers, according to past surgery



p = 0.0008

Fig. 7. Appearance of multiple primary cancers, depending on the number of pregnancies

higher education were represented in a greater number in the group of patients diagnosed with a second primary cancer. In that group, a significantly higher number of patients were classified (according to the ISCO-88 (COM classification) as "professionals". The result indicates how

important the individual's life and health history is when medical care based upon symptoms that may or may not suggest the presence of a cancer is sought. According to Tobiasz-Adamczyk, patients who have some disturbing signs suspect that grave illness because they have a prior knowledge of the telltale symptoms. Some patients, however, in spite of their knowledge of symptoms of cancer, may be incapable of proper diagnosis and evaluation of their condition. They may ignore or disregard the meaning of symptoms [23, 24].

Our analysis demonstrated that in the group of multiple primary cancers participants were mostly residents of large cities, usually with a population of over 500 thousand. That observation is probably associated with the influence of several factors. According to Tobiasz-Adamczyk, patients are more likely to seek medical attention when help is at hand [25]. Thus, easier access to medical institutions, services and state-of-art equipment and medical specialists may explain better detection of cancer among urban dwellers.

Availability of medical services is extremely important for patients who have uveal melanoma, because they have to be closely monitored for metastases. According to Eske-

Table 3. Results of logistic regression

| | Constant | Age | Higher or secondary education | Number of inhabitants over 500 thousand | Number of surgeries | Cancers among 1 st degree relatives |
|--|----------|-------|-------------------------------|---|---------------------|--|
| Assessment of the variable parameter | -6.434 | 0.026 | 1.171 | 1.384 | 3.840 | 0.584 |
| Significance level of the parameter – <i>p</i> | 0.000 | 0.097 | 0.000 | 0.004 | 0.000 | 0.087 |
| Odds ratio (unit) | | 1.026 | 3.226 | 3.991 | 46.539 | 1.794 |
| -95%CI | | 0.995 | 1.617 | 1.558 | 9.796 | 0.917 |
| +95%CI | | 1.058 | 6.436 | 10.226 | 221.096 | 3.503 |

Table 4. Results of logistic regression.

| | Constant | Age | Higher or secondary education | Number of inhabitants over 500 thousand | Number of surgeries | Cancers among 1 st /2 nd degree relatives |
|--|----------|-------|-------------------------------|---|---------------------|---|
| Assessment of the variable parameter | -6.717 | 0.030 | 1.133 | 1.342 | 3.762 | 0.716 |
| Significance level of the parameter – <i>p</i> | 0.000 | 0.058 | 0.001 | 0.006 | 0.000 | 0.039 |
| Odds ratio (unit) | | 1.030 | 3.104 | 3.827 | 43.017 | 2.047 |
| -95%CI | | 0.999 | 1.544 | 1.479 | 9.089 | 1.038 |
| +95%CI | | 1.063 | 6.199 | 9.902 | 203.595 | 4.035 |

lin *et al.*, detecting metastases of uveal melanoma in patients (who have not reported any symptoms yet) may vary in the case of testing using abdominal ultrasound and assessment of liver function (from the level of 59% for annual testing to over 95% in the case of semiannual testing [26]).

As for pregnancy, according to a literature review, hormonal changes significantly affect transformation of a choroidal naevus into a choroidal melanoma. In the group of 3,706 patients examined by Shields *et al.* [27], pregnant women accounted for 0.4% of respondents (16 people). The authors observed that only in seven of those pregnant women did tumors that were previously considered to be stable start to proliferate. Based on that observation, it was suggested that perhaps immune tolerance to the fetus promotes a greater propensity for tumor development and a non-pregnant state may preclude exacerbation of the disease.

Romanowska-Dixon suggested that pregnancy appears to constitute a risk factor for the worsening of a pre-existing aberrancy [28].

In the analyzed material none of the 140 included women having a diagnosis of uveal melanoma were pregnant. The period between the last pregnancy and the time of being treated in the Cracow Clinic ranged from 9 to 52 years in the group with multiple primary cancers, and from 3 to 57 years in the second group, with no identifiable primary cancer. Holly *et al.* [29], on the basis of their observations, found a correlation between decreased risk of uveal melanoma and increased parity.

Hartge *et al.* [30] observed an increased risk of uveal melanoma among women who had been pregnant or had previously had estrogen hormone replacement therapy. The risk decreased after surgical removal of the ovaries.

Among the patients analyzed, women with multiple primary cancers had significantly fewer pregnancies than patients who were not diagnosed with a second primary malignancy. That probably suggests a protective effect of pregnancy on the development of multiple cancers.

The described analysis was a retrospective chart review, not a prospective trial with clearly more rigorous reporting and data monitoring.

Conclusions

More common occurrence of malignant cancers in 1st and 1st and/or 2nd degree relatives of patients with uveal melanoma and other primary malignancies suggests existence of a common genetic factor in the development of different cancers.

A higher occurrence rate of multiple primary cancers among patients with better education and among patients working as “professionals” emphasizes the importance of knowledge of risk factors for development of a cancer, and of resulting more scrupulous observation of the primary neoplasm and more successful initiation of prophylactic interventions.

Persons living in cities (population > 500 K) are at higher risk for multiple primary cancers compared to those who live in rural areas. More frequent recognition of multiple primary cancers among persons living in cities (population > 500 K) may be associated with easier access to diagnosis, treatment, practitioners and equipment and with higher awareness of the role of pollution in the development of malignant cancer.

Fewer pregnancies in the past among women with multiple primary cancers, compared to women without

a second diagnosed primary malignancy, may suggest the protective effect of pregnancy against the development of multiple primary cancers.

The authors declare no conflict of interests.

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